## REMARKS

Claims 1, 2, and 13 are pending in the instant application. Claims 1 and 13 have been amended. Claim 1 has been amended to include the limitations of claim 2. Further, claim 1 has been amended to recite that the cell is contacted with HIV or infected with HIV, explicitly reciting that infection or replication is inhibited in a cell contacted with or infected with HIV. Applicant submits that HIV infection or replication cannot be attenuated in a cell not contacted with or infected with HIV. The amendment is supported throughout the specification, for example in the paragraph bridging pages 62-63 of the specification. Further, claim 35 is supported throughout the specification, e.g., the paragraph bridging pages 62-63 of the specification, and is noted in the Office Action to be enabled by the specification. The amendment includes no new matter.

*Amendment to the Specification*

The Office Action has objected to the form of the amendment made to the specification in the prior response to Office Action. Applicant thanks the Examiner for accepting the prior response despite the error in form. Applicant has provided a marked up amendment to the specification above wherein the new text is underlined. No new matter is added by the amendment.

*Rejection of claims under 35 U.S.C. §112, first paragraph*

Enablement

The Office Action has maintained the rejection of claims 1, 2, and 13 under 35 U.S.C. 112, first paragraph for allegedly not being enabled for methods of attenuating the transmission or infection of HIV using any CDDO ***derivative***, or for methods of treating AIDS in an individual.

Applicant respectfully disagrees and points out that the ***claims are not drawn to CDDO derivatives***, but instead to CDDO, di-CDDO, or a salt thereof. A salt of a compound would not be understood to be a derivative of the compound. Therefore, the

rejection must fall. In fact, the rejection is contrary to the remarks made in the prior Office Action. Specifically, the sentence bridging pages 4-5 of the Office Action mailed on December 2, 2009 states:

> While the application as filed adequately describes a single triterpenoid, CDDO (pp 62-63) that would be recognized as having the function required by the claims, [*sic*] species alone would not enable one of skill to predict the structure of any other species within the genus having these functions.

Therefore, it is acknowledged that the specification is enabling for the methods as now claimed.

Withdrawal of the rejection is respectfully requested. Moreover, as the rejection is contrary to the statements in the prior Office Action, the finality of the instant Office Action should be withdrawn.

Applicant notes that on page 3 the instant Office Action states that "the specification [is]... enabling for methods of reducing HIV replication and levels in cells in culture and for reducing viral replication and levels in an individual", providing support and indicating enablement for newly added claim 35.

Applicant respectfully disagrees that the specification does not provide support for methods of inhibition of infection of cells with HIV and inhibition of replication of HIV in cells using CDDO, and di-CDDO. Specifically, Figure 5 shows results from experiments in which cells were pretreated with CDDO or di-CDDO (A-C) prior to exposure to HIV or treated after infection (D-F) with HIV. Further, although a different inhibitor (siRNA) was used in the experiments performed in Figure 6, treatment of cells five days prior to contacting the cells with HIV resulted in an attenuation of infection of the cells. Inhibition of infection would clearly inhibit transmission. Further, immediate inhibition of replication would also inhibit transmission. These results provide a reasonable expectation that CDDO and di-CDDO can attenuate infection by and transmission of HIV, supporting the claimed methods.

*Rejection of claims under 35 U.S.C. §102*

The Office Action has rejected claims 1 and 2 under 35 U.S.C. §102 for allegedly being anticipated by Place et al. (July 2003) "The novel synthetic triterpenoid, CDDO-imidazolide, inhibits inflammatory response and tumor growth in vivo" *Clin. Cancer. Res.* 9(7): 2798-806. Applicant respectfully disagrees.

The Office Action asserts that as the preamble is given no patentable weight, "the claims read on any method of administering CDDO to any cell in vitro or in vivo for any purpose." Applicant submits that as the preamble breathes life into the claim that it must be considered a limitation of the claim. Moreover, the method steps recited after the preamble can only be practiced on a cell that is contacted with or infected with HIV. In the absence of an HIV infection, or a potential HIV infection, reduction of replication or attenuation of infection would not be possible.

The Office Action states that Place et al. disclosed a method of administering CDDO to human cancer cells in culture. There is no teaching or suggestion in Place that the cells are contacted with or infected with HIV. As the cited reference does not teach all of the elements of the claim, now clearly recited in the body of the claim, the reference cannot anticipate the claim. Withdrawal of the rejection is respectfully requested.

The Office Action has rejected claims 1, 2, and 13 under 35 U.S.C. 102(e) for allegedly being anticipated by Salcedo et al. (WO 2004/016753).

Applicant respectfully disagrees and maintains that the method of Salcedo requires the use of antibodies, and that Salcedo does not provide a method as claimed in which the p21 inhibitor could attenuate infection or replication by at least 50% as claimed. Applicant notes that in each of the claims recite that "said [p21] inhibitor is provided in an amount and duration sufficient ***to cause an attenuation of at least about 50%***" in transmission of infection or replication. Therefore although the claims do not preclude co-administration with other agents, as clearly greater than 50% inhibition

of transmission or replication would be desirable in a therapeutic agent, based on the teachings of Salcedo, one would not expect that such a high level of inhibition would be possible using CDDO or di-CDDO alone.

The Office Action relies on the teachings considered to be inherent to Salcedo. Applicant submits that a rejection for anticipation cannot rely on probabilities and possibilities, but must rely on results that would inherently flow from the method provided in the cited art. The teachings related to CDDO are only in relation to use as a combination therapeutic. Specifically, Salcedo states:

> In one embodiment, an antibody composition of the invention is administered in combination with a histone deacetylase inhibitor (e.g., depsipeptide (e.g., FK-288 and FR901228), MS-275, and the triterpenoid 2-cyano-3,12-dioxooleana-1,9-dien-28-oic acid (CDDO) or other molecules related to CDDO, valproic acid, suberoylanilide hydroxamic acid (SAHA), pyroxamide, trapoxin, (depsipeptide), and N-acetyl dinaline (CI-994).

Prior to the filing of the instant application CDDO was known as a cancer therapeutic, not for attenuating transmission or replication of HIV, particularly to the level claimed. In fact, Salcedo lists CDDO as a chemotherapeutic agent in the heading on page 206 immediately before paragraph 459. Salcedo cannot be understood to teach the use of CDDO with cells contacted with or infected with HIV for the attenuation of transmission of HIV infection or HIV replication.

Although Salcedo does teach that the antibodies provided therein can be used for the treatment of HIV, the list of diseases that can allegedly be treated with the antibodies is extensive and includes:

> cancer (e.g., immune cell related cancers, breast cancer, prostate cancer, ovarian cancer, follicular lymphoma, cancer associated with mutation or alteration of p53, brain tumor, bladder cancer, uterocervical cancer, colon cancer, colorectal cancer, non-small cell carcinoma of the lung, small cell carcinoma of the lung, stomach cancer, etc.), lymphoproliferative disorders (e.g., lymphadenopathy),

> microbial (e.g., viral, bacterial, etc.) infection (e.g., HIV-1 infection, HIV-2 infection, herpesvirus infection (including, but not limited to, HSV-1, HSV-2, CMV, VZV, HHV-6, HHV-7, EBV), adenovirus infection, poxvirus infection, human papilloma virus infection, hepatitis infection (e.g., HAV, HBV, HCV, etc.), Helicobacter pylori infection, invasive Staphylococcia, etc.), parasitic infection, nephritis, bone disease (e.g., osteoporosis), atherosclerosis, pain, cardiovascular disorders (e.g., neovascularization, hypovascularization or reduced circulation (e.g., ischemic disease (e.g., myocardial infarction, stroke, etc.))), AIDS, allergy, inflammation, neurodegenerative disease (e.g., Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, pigmentary retinitis, cerebellar degeneration, etc.), graft rejection (acute and chronic), graft vs. host disease, diseases due to osteomyelodysplasia (e.g., aplastic anemia, etc.), joint tissue destruction in rheumatism, liver disease (e.g., acute and chronic hepatitis, liver injury, and cirrhosis), autoimmune disease (e.g., multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, autoimmune lymphoproliferative syndrome (ALPS), immune complex glomerulonephritis, autoimmune diabetes, autoimmune thrombocytopenic purpura, Grave's disease, Hashimoto's thyroiditis, etc.), cardiomyopathy (e.g., dilated cardiomyopathy), diabetes, diabetic complications (e.g., diabetic nephropathy, diabetic neuropathy, diabetic retinopathy), influenza, asthma, psoriasis, glomerulonephritis, septic shock, and ulcerative colitis.

Therefore, at best, Salcedo can be understood to teach that there are many known drugs and many known diseases. The possibility that a subject suffering from HIV may also be suffering from Kaposi's sarcoma and may possibly be treated with an antibody of Salcedo, in combination with CDDO in an amount sufficient to inhibit HIV replication by 50%, is not sufficient to make a rejection for anticipation. Moreover, as Salcedo teaches that CDDO is a chemotherapeutic agent, there could be no motivation to administer CDDO to prevent infection by HIV. Salcedo cannot be understood to teach the instantly claimed method.

Further, as discussed below, those being susceptible to or having HIV infection cannot inherently be understood to have KS or any other form of cancer. Similarly, those with cancer cannot be understood to inherently be susceptible to or have HIV.

Withdrawal of the rejection is respectfully requested.

*Rejection of claims under 35 U.S.C. §103*

The Office Action has rejected claims Claims 1, 2, and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xu et al. (US Patent 5,916,919) "Retrovirus protease inhibitors" and Salcedo et al. (WO 2004/016753) "Antibodies that immunospecifically bind to TRAIL receptors," the combination in view of Nasti et al. (1997) "Malignant tumors and AIDS" Biomed. Pharmacother. 51:243-251.

The Office Action asserts that Xu teaches compounds structurally related to CDDO, but does not specifically teach CDDO; that Salcedo "Salcedo et al. had expressly suggested using a combination of CDDO and TRAIL receptor immunospecific antibodies for treating HIV infection and AIDS"; and that Nasti teaches that Kaposi's sarcoma (KS) is 2000 times more common in AIDS infected individuals than in the general population. Based on the combined teachings of the references, the Office Action asserts that the instantly claimed invention would be obvious in view of the cited art.

Applicant respectfully disagrees.

First, the teaching of Xu of compounds similar to CDDO does not make obvious CDDO or di-CDDO as claimed. The Court has addressed the issue of obviousness in chemical cases since the decision of *KSR*. Specifically the Court stated:

> While the *KSR* Court rejected a rigid application of the... TSM test in an obviousness inquiry, the Court acknowledged the importance of identifying ***'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the***

> ***claimed new invention does'*** in an obviousness determination.
>
> When there is a design need or market pressure to solve a problem and there is a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1732. * * * That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, ***the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation***. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. *Takeda Chemical Industries Ltd. v. Alphapharm Pty.* 492 F.3d 1350 (Fed. Cir. 2007) [emphasis added]

The Office Action provides no reason that would have prompted one of ordinary skill to modify the structures provided by Xu to provide CDDO and di-CDDO as claimed.

Second, Salcedo does not expressly suggest using a combination of CDDO and TRAIL receptor antibodies for treating HIV infections and AIDS. As discussed above, Salcedo teaches that CDDO is used to treat cancer, and TRAIL receptor antibodies can be used in combination with chemotherapeutic agents for treating cancer. Trial receptor antibodies can also be used for treating HIV infections. As noted in the Office Action, the teachings related to CDDO are in paragraph 476, and the teachings related to the treatment, prevention, amelioration and/or cure of Kaposi's sarcoma are in paragraph 384. The list of diseases and chemotherapeutic compounds taught by Salcedo is immense. There can be no motivation to select a compound taught to be a chemotherapeutic agent for the attenuation of HIV infection or replication. Moreover, as claim 1 is drawn to methods to reduce transmission of HIV, the subject would not have an HIV infection and would not have cancer, particularly KS which is an opportunistic infection associated almost exclusively with immunosupression.

The alleged teachings of Nasti that KS is 2000 fold more prevalent in those with HIV infection than in the general population does not mean that KS is common even in

those with HIV infection and AIDS. Moreover, claim 1 which is drawn to methods of reducing transmission of HIV would typically not include subjects already suffering from HIV. In the attached article by the International Collaboration on HIV and Cancer entitled "Highly Active Antiretroviral Therapy and Incidence of Cancer in Human Immunodeficiency Virus-Infected Adults" published in the *Journal of the National Cancer Institute* in 2000 (92:1823-1830) shows that the incidence of KS even in those with HIV was very low as of 1997 after the introduction of highly active anti-retroviral therapy (HAART), about three incidences per 1000 person-years. This rate was significantly lower than that prior to the introduction of HAART, around 7-8 per 1000 person years (see Figure 1a). Looking at incidence of KS from 1992-1999, including years prior to widespread use of HAART, 1679 incidences of KS were diagnosed in 47,936 study subjects, resulting in a frequency of about 3.5%. With the introduction of HAART, the incidence is likely now lower. Although much higher than the general population, the rate could not be considered sufficiently high to prophylactically treat subjects for the disease. It would have been understood by one of skill in the art at the time of filing of the instant application that improved anti-retroviral therapy was effective against KS based on the study discussed above. Based on the knowledge of those of skill in the art, a more effective HIV therapeutic would likely have been considered to be a more effective method to reduce the incidence of KS or to treat KS. KS which is an opportunistic infection. As chemotherapeutic agents frequently have immunosuppressive activity, one of skill in the art would not look to therapeutics that suppress the immune system for the treatment of KS.

Applicant submits that the instantly claimed invention cannot be obvious in view of the cited art. Withdrawal of the rejection is respectfully requested.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: July 27, 2010

Respectfully submitted,
Electronic signature: /Colleen McKiernan, Ph.D./
Colleen McKiernan, Ph.D.
Registration No.: 48,570
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 517-5555
Attorneys/Agents For Applicant

Customer No. 21874